General

Guideline Title

Guideline for the prevention of acute chemotherapy-induced nausea and vomiting in pediatric cancer patients: a focused update.

Bibliographic Source(s)

Patel P, Robinson PD, Thackray J, Flank J, Holdsworth MT, Gibson P, Orsey A, Portwine C, Freedman J, Madden JR, Phillips R, Sung L, Dupuis LL. Guideline for the prevention of acute chemotherapy-induced nausea and vomiting in pediatric cancer patients: a focused update. Pediatr Blood Cancer. 2017 Oct;64(10) [48 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Dupuis LL, Boodhan S, Holdsworth M, Robinson PD, Hain R, Portwine C, O'Shaughnessy E, Sung L. Guideline for the prevention of acute nausea and vomiting due to antineoplastic medication in pediatric cancer patients. Toronto (ON): Pediatric Oncology Group of Ontario (POGO); 2012. 199 p. [129 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

= Poor = Fair = Good = Very Good = Excellent

Assessment	Standard of Trustworthiness
YES	Disclosure of Guideline Funding Source
	Disclosure and Management of Financial Conflict of Interests

	Guideline Development Group Composition
YES	Multidisciplinary Group
YES	Methodologist Involvement
▮▯▯▯▯	Patient and Public Perspectives
	Use of a Systematic Review of Evidence
▮▮▮▮▮	Search Strategy
▮▮▮▮▮	Study Selection
▮▮▮▮▮	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
▮▮▮▯▯	Grading the Quality or Strength of Evidence
▮▮▮▮▯	Benefits and Harms of Recommendations
▮▮▮▮▮	Evidence Summary Supporting Recommendations
▮▮▮▯▯	Rating the Strength of Recommendations
▮▮▮▮▮	Specific and Unambiguous Articulation of Recommendations
▮▮▮▮▯	External Review
▮▯▯▯▯	Updating

Recommendations

Major Recommendations

Strength of recommendations (Strong, Weak) and quality of evidence (High, Moderate, Low, Very Low) are defined at the end of the "Major Recommendations" field.

Health Question 1: What pharmacological interventions provide optimal control of acute chemotherapy-induced nausea and vomiting (CINV) in children receiving highly emetogenic chemotherapy (HEC)?

Recommendations

Recommendation 1.1: The Panel recommends that children ≥6 months old receiving HEC which is *not* known or suspected to interact with aprepitant receive granisetron or ondansetron or palonosetron + dexamethasone + aprepitant. (Strong Recommendation, Moderate Quality Evidence)
Recommendation 1.2: The Panel recommends that children <6 months old receiving HEC receive granisetron or ondansetron or palonosetron + dexamethasone. (Strong Recommendation, Moderate Quality Evidence)
Recommendation 1.3: The Panel recommends that children ≥6 months receiving HEC, which is known or suspected to interact with aprepitant, receive granisetron or ondansetron or palonosetron + dexamethasone. (Strong Recommendation, Moderate Quality Evidence)

Recommendation 1.4: The Panel recommends that children ≥6 months old receiving HEC, which is *not* known or suspected to interact with aprepitant, and who *cannot* receive dexamethasone for CINV prophylaxis receive palonosetron + aprepitant. (Strong Recommendation, Moderate Quality Evidence)
Recommendation 1.5: The Panel suggests that children <6 months old receiving HEC and who cannot receive dexamethasone for CINV prophylaxis receive palonosetron. (Weak Recommendation, Moderate Quality Evidence)
Recommendation 1.6: The Panel suggests that children receiving HEC, which is known or suspected to interact with aprepitant, and who *cannot* receive dexamethasone receive palonosetron. (Weak Recommendation, Moderate Quality Evidence)

Health Question 2: What pharmacological interventions provide optimal control of acute CINV in children receiving moderately emetogenic chemotherapy (MEC)?

Recommendations

Recommendation 2.1: The Panel recommends that children receiving MEC receive granisetron or ondansetron or palonosetron + dexamethasone. (Strong Recommendation, Moderate Quality Evidence)
Recommendation 2.2: The Panel suggests that children ≥6 months receiving MEC who *cannot* receive dexamethasone for CINV prophylaxis receive granisetron or ondansetron or palonosetron + aprepitant. (Weak Recommendation, Moderate Quality Evidence)
Recommendation 2.3: The Panel suggests that children <6 months receiving MEC who *cannot* receive dexamethasone for CINV prophylaxis receive palonosetron. (Weak Recommendation, Moderate Quality Evidence)
Recommendation 2.4: The Panel suggests that children receiving MEC, which is known or suspected to interact with aprepitant, and who *cannot* receive dexamethasone receive palonosetron. (Weak Recommendation, Moderate Quality Evidence)

Health Question 3: What doses of aprepitant and palonosetron are known to be effective in children receiving chemotherapy?

Recommendations

Recommendation 3.1: The Panel suggests the following aprepitant dose for children ≥6 months:
Day 1: 3 mg/kg (maximum: 125 mg) by mouth (PO) × 1.
Days 2 and 3: 2 mg/kg (maximum: 80 mg) PO once daily.
(Weak Recommendation, Moderate Quality Evidence)

Recommendation 3.2: The Panel suggests the following palonosetron dose for children:
1 month to <17 years: 0.02 mg/kg intravenous (IV) once (maximum: 1.5 mg/dose) prechemotherapy.
≥17 years: 0.25 mg/dose IV or 0.5 mg/dose PO once prechemotherapy.
(Weak Recommendation, Moderate Quality Evidence)

Definitions

Quality of Evidence

High Quality	Further research is very unlikely to change confidence in the estimate of effect.
Moderate Quality	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low Quality	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low Quality	Any estimate of effect is very uncertain.

Strength of Recommendations

Strong Recommendation	When using Grading of Recommendations Assessment, Development and Evaluation (GRADE), panels make strong recommendations when they are confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.
Weak Recommendation	Weak recommendations indicate that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is less confident.

Clinical Algorithm(s)

A clinical algorithm titled "Summary of recommendations regarding antiemetic agent selection for prevention of acute chemotherapy-induced nausea and vomiting (CINV) in children" is provided in Figure 1 of the original guideline document.

Scope

Disease/Condition(s)

Acute chemotherapy-induced nausea and vomiting (CINV)

Note: Nausea is defined as the subjective sensation that one might vomit.

Guideline Category

Prevention

Treatment

Clinical Specialty

Oncology

Pediatrics

Preventive Medicine

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To optimize acute chemotherapy-induced nausea and vomiting (CINV) control in children by providing guidance on the use of aprepitant and palonosetron to healthcare professionals who care for children with cancer or for those receiving chemotherapy for hematopoietic stem cell transplant conditioning

Target Population

Chemotherapy-naïve cancer patients 1 month to 18 years of age

Interventions and Practices Considered

1. Antiemetic agents
    - Ondansetron
    - Granisetron
    - Dexamethasone
    - Aprepitant
    - Palonosetron
2. Combination treatments

Major Outcomes Considered

- Optimal control of acute chemotherapy-induced nausea and vomiting (CINV)
- Drug-related adverse events

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Three systematic reviews were conducted in consultation with a library scientist. The database search strategies, eligibility criteria, and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowcharts for each systematic review are provided in the online Supplementary Material Sections B–D (see the "Availability of Companion Documents" field). Two reviewers independently screened the titles and abstracts, evaluated the full text of potentially relevant citations for eligibility, and assessed the risk of bias of included randomized trials using the Cochrane Collaboration tool. Disagreements were resolved by a third reviewer. The three systematic reviews were:

> Primary studies of aprepitant or palonosetron describing the rate of chemotherapy-induced nausea and vomiting (CINV) control in children;
> Meta-analyses evaluating palonosetron compared to other 5-hydroxytryptamine type 3 ($5\text{-}HT_3$) antagonists for acute CINV prophylaxis in adults or children; and
> Primary studies describing palonosetron pharmacokinetic disposition.

The OvidSP platform was used to search MEDLINE, Medline in Process and EMBASE for all searches, for articles indexed from database inception up to June 21, 2016, March 29, 2016, and May 5, 2016, respectively.

Number of Source Documents

See Supplementary Figures S1 to S3 (see the "Availability of Companion Documents" field) for PRISMA flow charts detailing the study selection process.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

High Quality	Further research is very unlikely to change confidence in the estimate of effect.
Moderate Quality	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low Quality	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low Quality	Any estimate of effect is very uncertain.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence tables were compiled to summarize the findings of all included studies and organized by chemotherapy emetogenicity (minimal, low, moderate, and high) based on the pediatric emetogenicity classification guideline or, when this was not possible, by the chemotherapy emetogenicity classification used by the authors of the included studies. For studies where subjects received chemotherapy of different levels of emetogenicity (e.g., highly emetogenic chemotherapy [HEC] or moderately emetogenic chemotherapy [MEC]) and where study investigators did not report chemotherapy-induced nausea and vomiting (CINV) control rates for these two groups separately, the extracted data were categorized under the lower emetogenicity level.

Evidence summaries of adverse events were restricted to those reported in included randomized trials, since adverse event reporting in these studies was more likely to be completed in a systematic fashion.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Recommendations were developed based on the evidence identified from the systematic reviews and refined through panel discussions. The associated potential health benefits versus risks were considered for each recommendation. Strong recommendations (i.e., most individuals should receive the

recommended intervention) were made when the panel was certain that the potential benefits of the recommended intervention outweighed the risk of harm. Differences in opinion were resolved by consensus. The quality of evidence and strength of recommendations were assessed using the Grades of Recommendation Assessment, Development and Evaluation system by one author and confirmed through discussion by the remaining panel members. If consensus could not be reached, a decision was made by the majority of panel members by a vote.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong Recommendation	When using Grading of Recommendations Assessment, Development and Evaluation (GRADE), panels make strong recommendations when they are confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.
Weak Recommendation	Weak recommendations indicate that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is less confident.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

External Review

A draft version of the guideline was reviewed by international experts in pediatric chemotherapy-induced nausea and vomiting (CINV). The committee considered the responses received before finalizing the recommendations (see Supplementary Tables S15 and S16 ["see the Availability of Companion Documents" field]).

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Optimized control and prevention of acute chemotherapy-induced nausea and vomiting (CINV)

Potential Harms

Drug-related adverse events. Refer to Supplementary Tables S2 to S7 (see the "Availability of Companion Documents" field) for information on specific adverse events.

Qualifying Statements

Qualifying Statements

- Significant changes have been made to the recommendations in light of new evidence supporting the use of aprepitant and palonosetron in children. However, extensive evidence gaps remain. Continual appraisal of the evidence and prospective evaluation of patient outcomes that are achieved with the implementation of these recommendations are required. Furthermore, to ensure that control of acute chemotherapy-induced nausea and vomiting (CINV) in children is optimized, future work must address critical evidence gaps.
- Aprepitant is not recommended for use in children less than 6 months of age because it has not been studied in this age group for the purpose of chemotherapy-induced nausea and vomiting (CINV) prophylaxis.

Implementation of the Guideline

Description of Implementation Strategy

Implementation Considerations

While motivated by chemotherapy-induced nausea and vomiting (CINV) control optimization and safety, the panel recognized that the cost of aprepitant and palonosetron may be a barrier to the implementation of these recommendations. In jurisdictions where cost is a barrier to using palonosetron 0.02 mg/kg/dose and compliance with the dose approved by regulatory authorities is not a concern, it may be reasonable to initiate palonosetron at the recommended dose with a patient's first chemotherapy block and, depending on the patients' CINV control, to administer a lower dose with a future chemotherapy block. Administration of ondansetron or granisetron may also be reasonable. Patient and institutional values, preferences and resources should be considered when implementing guideline recommendations.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2017 Oct

Guideline Developer(s)

Pediatric Oncology Group of Ontario - Professional Association

Source(s) of Funding

The development of this guideline was financially supported by the Pediatric Oncology Group of Ontario. The funder did not influence the recommendations of the clinical practice guideline.

Guideline Committee

Chemotherapy-induced Nausea and Vomiting (CINV) Guideline Panel

Composition of Group That Authored the Guideline

Panel Members: Priya Patel, Department of Pharmacy, The Hospital for Sick Children, Toronto, Canada, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada; Paula D. Robinson, Pediatric Oncology Group of Ontario, Toronto, Canada; Jennifer Thackray, Memorial Sloan Kettering Cancer Center, New York, New York; Jacqueline Flank, Department of Pharmacy, The Hospital for Sick Children, Toronto, Canada; Mark T. Holdsworth, College of Pharmacy, University of New Mexico, Albuquerque, New Mexico; Paul Gibson, Pediatric Hematology/Oncology, Children's Hospital, London Health Sciences Centre, London, Canada; Andrea Orsey, Division of Pediatric Hematology/Oncology, Connecticut Children's Medical Center, Hartford, Connecticut, Department of Pediatrics, University of Connecticut School of Medicine, Farmington, Connecticut; Carol Portwine, Division of Hematology/Oncology, Department of Pediatrics, McMaster University, Hamilton, Canada; Jason Freedman, Division of Oncology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, Department of Pediatrics, Perelman School of Medicine,

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Financial Disclosures/Conflicts of Interest

The membership of the interprofessional Chemotherapy-Induced Nausea and Vomiting (CINV) Guideline Panel and conflict of interest declarations are provided in the online Supplementary Material Section A (see the "Availability of Companion Documents" field). No panel member had a conflict of interest that precluded participation.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Dupuis LL, Boodhan S, Holdsworth M, Robinson PD, Hain R, Portwine C, O'Shaughnessy E, Sung L. Guideline for the prevention of acute nausea and vomiting due to antineoplastic medication in pediatric cancer patients. Toronto (ON): Pediatric Oncology Group of Ontario (POGO); 2012. 199 p. [129 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Pediatric Blood and Cancer Web site .

Availability of Companion Documents

The following is available:

> Supplemental appendix. Guideline for the prevention of acute chemotherapy-induced nausea and vomiting due in pediatric cancer patients: a focused update. Toronto (ON): Pediatric Oncology Group of Ontario (POGO); 58 p. Available from the Pediatric Blood and Cancer Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on November 26, 2012. The information was verified by the guideline developer on January 15, 2013. This NGC summary was updated by ECRI Institute on October 11, 2017. The updated information was not verified by the guideline developer.

This NEATS assessment was completed by ECRI Institute on September 7, 2017. The guideline developer did not acknowledge or provide confirmation for this NEATS assessment.

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